

## II. REMARKS

### Formal Matters

Claims 2-7, 11, and 12 are pending after entry of the amendments set forth herein.

Claims 2-7 were examined and were rejected. Claim 8 was withdrawn from consideration.

Claims 11 and 12 were allowed.

Claim 8 is canceled without prejudice to renewal, without intent to acquiesce to any rejection, and without intent to surrender any subject matter encompassed by the canceled claim. Applicants expressly reserve the right to pursue any canceled subject matter in one or more continuation and/or divisional applications.

Applicants respectfully request reconsideration of the application in view of the remarks made herein.

### Allowable subject matter

Applicants note with gratitude that claims 11 and 12 were deemed allowable.

### Rejection under 35 U.S.C. § 112, first paragraph

Claims 2-7 were rejected under 35 U.S.C. § 112, first paragraph, as allegedly lacking enablement.

The Office Action stated that the specification does not reasonable provide enablement for making a deletion in the entire range of 15 kb to 3000 kb. Applicants respectfully traverse the rejection.

As a first note, instant claim 2 recites a method for obtaining a mammalian cell comprising a genomic deletion in a range of from about 50 kb to about 3000 kb.

The law regarding enablement of inventions is clear: “[t]he test of enablement is whether one reasonably skilled in the art could make or use the invention from the disclosures in the patent coupled with information known in the art without undue experimentation.”<sup>1</sup>

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<sup>1</sup> *United States v. Teletronics, Inc.*, 8 USPQ 2d 1217, 1233 (Fed. Cir. 1988), *cert. denied*, 490 U.S. 1046 (1989). See also *Genentech, Inc. v. Novo Nordisk*, 42 USPQ 2d 1001 (Fed. Cir. 1997), *cert. denied*, 522 U.S. 963 (1997); *Scripps Clinic and Research Foundation v. Genentech, Inc.*, 18 USPQ 2d 1001 (Fed. Cir. 1991).

To aid in determinations of enablement, courts have identified eight factors for consideration: (a) the quantity of experimentation necessary; (b) the amount of direction or guidance presented; (c) the presence or absence of working examples; (d) the nature of the invention; (e) the state of the prior art; (f) the relative skill of those in the art; (g) the predictability or unpredictability of the art; and (h) the breadth of the claims.<sup>2</sup>

The instant specification provides ample guidance for those skilled in the art to practice the invention as claimed. The specification describes how to make a replacement targeting construct that includes a selectable marker and two regions of sequences that are homologous to the 5' and 3' flanking sequences of the targeted locus; how to introduce such a construct into a host cell; and how to select cells containing a deletion. Specification, page 6, lines 9-30; and page 8, lines 6-20. The specification provides a working example of the method. Specification, Example 1. The Example describes generation of a 55 kb deletion in a locus. Those skilled in the art, using the instant specification as guidance, could have readily made deletions of sizes larger than 55 kb.

The instant specification discusses the method as claimed in which the targeting construct includes two regions of sequences that are homologous to the 5' and 3' flanking sequences of the wild-type target locus, and indicates that the homologous sequences are at least about 500 base pairs. Specification, page 6, lines 28-30.

**a) the quantity of experimentation necessary**

The courts have clearly taught that the fact that experimentation may be complex does not necessarily make it undue, if the art typically engages in such experimentation. For example, see MPEP §2164.01.<sup>3</sup>

As the court explained<sup>4</sup>:

“[A] considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed.”

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<sup>2</sup> *Ex Parte Forman*, 230 USPQ 546, 547 (Bd.Pat.App & Interf. 1986); and, *In re Wands*, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

<sup>3</sup> See also *In re Certain Limited-Charge Cell Culture Microcarriers*, 221 USPQ 1165, 1174 (Int'l Trade Comm'n 1983), *aff'd sub nom.*, *Massachusetts Institute of Technology v. A.B. Fortia*, 227 USPQ 428 (Fed. Cir. 1985).

<sup>4</sup> *In re Wands* 8 USPQ 2d at 1404

Practitioners in the chemical and molecular biology arts frequently engage in extensive modification of reaction conditions and complex and lengthy experimentation where many factors must be varied to succeed in performing an experiment or in producing a desired result. The Federal Circuit has found that such extensive experimentation is not undue in the molecular biology arts. For example, the court concluded that extensive screening experiments, while being voluminous, were not undue in view of the art which routinely performs such long experiments.<sup>5</sup>

The claimed method recites the steps: a) modifying the genome of mammalian cells comprising a wild-type target locus by introducing a construct comprising two regions of sequences that are homologous to the 5' and 3' flanking sequences of said wild-type target locus, wherein said homologous sequences are at least about 500 base pairs; b) identifying cells containing said deletion by selecting cells containing a selectable marker present in said construct; and c) recovering mammalian cell comprising said deletion. The only experiments, if any, that need be performed to enable the entire scope of the claim are those designed to create a construct having the recited features, and to determine whether a cell population includes a genomic deletion in the recited size range. The generation of constructs having the recited features, and identifying cells that possess a genomic deletion in the recited size range are readily accomplished through routine experimentation, typically employing nothing more than performing the same methods disclosed in the specification, e.g., in the Example. Since these experiments are routine, no undue experimentation is required.

**(b) the amount of direction or guidance presented**

As discussed above, the specification describes how to make a replacement targeting construct that includes a selectable marker and two regions of sequences that are homologous to the 5' and 3' flanking sequences of the targeted locus; how to introduce such a construct into a host cell; and how to select cells containing a deletion. Specification, page 6, lines 9-30; and page 8, lines 6-20. The specification provides a working example of the method. Specification, Example 1. The Example describes generation of a 55 kb deletion in a locus. The instant specification discusses the method as claimed in which the targeting construct includes two regions of sequences that are homologous to the 5'

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<sup>5</sup> *Hybritech v. Monoclonal Antibodies, Inc.* 231 USPQ 81 (Fed. Cir. 1986)

and 3' flanking sequences of the wild-type target locus, and indicates that the homologous sequences are at least about 500 base pairs. Specification, page 6, lines 28-30.

**(c) the presence or absence of working examples**

Compliance with the enablement requirement under Section 35 U.S.C. §112, first paragraph does not require or mandate that a specific example be disclosed. The specification need not contain a working example if the invention is otherwise disclosed in such a manner that one skilled in the art would be able to practice the invention without undue experimentation.<sup>6</sup> Furthermore, "Nothing more than objective enablement is required, and therefore it is irrelevant whether [a] teaching is provided through broad terminology or illustrative examples."<sup>7</sup> Nevertheless, the specification does provide a working example.

**(f) the relative skill of those in the art:**

The relevant ordinarily skilled artisan is generally a skilled laboratory technician with experience in molecular biology and/or a scientist with the equivalent of a doctoral degree in molecular biology techniques. Furthermore, such artisans are required to keep abreast of the latest technology through continuing education and reading of scientific journal articles. As such, the skill level of those developing and using methods for manipulating DNA and performing cell-based assays is high.

**(g) the predictability or unpredictability of the art**

The instant specification provides a working example of a 55 kb deletion. However, the courts have clearly taught that the specification does not have to disclose every species of a genus that would work and every species that would not work.

The court has very clearly explained<sup>8</sup>:

"To require such a complete disclosure would apparently necessitate a patent application or applications with thousands of catalysts....More importantly, such a requirement would force an inventor seeking adequate patent protection to carry out a prohibitive number of actual experiments. This would tend to discourage

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<sup>6</sup> *In re Borkowski*, 164 USPQ at 645.

<sup>7</sup> *In re Robins* 166 USPQ 552 at 555 (CCPA 1970).

<sup>8</sup> *In re Angstadt*, 190 USPQ at 218.

inventors from filing patent applications in an unpredictable area since the patent claims would have to be limited to those embodiments which are expressly disclosed. A potential infringer could readily avoid literal infringement of such claims by merely finding another analogous catalyst complex which could be used ....”

The claims of the instant application encompass a method for making genomic deletions in the size range of 50 kb to 3000 kb. Because every species in a genus does not have to be tested for a genus to be enabled, extensive disclosure or guidance of every species of a genus does not have to be provided for a genus of this scope to be enabled.

In sum, the amount of experimentation required to carry out the instant methods as claimed would not be undue because a) a working example has been provided, b) guidance is given on how to make deletion constructs and how to identify cells having a genomic deletion in the recited size range, and c) one of skill in the art would be able to perform the experiments as a matter of routine to identify cells having a genomic deletion in the recited size range. The specification therefore provides sufficient enablement such that one of ordinary skill in the art would be able to practice the invention without undue experimentation.

Applicants submit that the rejection of claims 2-7 under 35 U.S.C. §112, first paragraph, has been adequately addressed in view of the remarks set forth above. The Examiner is thus respectfully requested to withdraw the rejection.


### III. CONCLUSION

Applicants submit that all of the claims are in condition for allowance, which action is requested. If the Examiner finds that a telephone conference would expedite the prosecution of this application, the Examiner is invited to telephone the undersigned at the number provided.

The Commissioner is hereby authorized to charge any underpayment of fees associated with this communication, including any necessary fees for extensions of time, or credit any overpayment to Deposit Account No. 50-0815, order number ABG: X001CON3.

Respectfully submitted,  
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